

Letters to the Editor

Age at First Birth and Risk of Epithelial Ovarian Cancer

SIR: La Vecchia and his co-workers recently reported in this Journal that later age at first birth increased the risk of ovarian cancer and that this effect explained much of the apparent relation between lower parity and higher risk.¹ We have estimated the effects of age at first birth and parity on ovarian cancer risk, using interview data from two hospital-based case-control studies, one conducted in 1974-77² and one in 1978-81 in Metropolitan Washington, DC. These data (tables 1, 2) show a marked and consistent reduction in risk with greater parity, after adjustment in age at first birth. By contrast, the estimated incidence ratio does not vary markedly or consistently according to age at first birth. Additional adjustment for age at diagnosis did not alter these findings.

We can offer no simple explanation for the difference between La Vecchia's findings (table 3) and ours. Our studies included only histologically confirmed, primary newly diagnosed epithelial cancers, including both carcinoma of low malignant potential and obviously malignant tumors. We used hospital controls, excluding

patients with bilateral oophorectomy or with admission diagnoses related to potential ovarian cancer risk factors (e.g., gynecologic diseases, heart disease, gall bladder disease). La Vecchia's study followed a similar protocol, but included all women under the age of 75 years, whereas our studies included all women under the age of 80 years. La Vecchia's data showed a somewhat stronger effect of age at first birth among women under the age of 50 years. Our data showed no increased risk with later age at first birth in women under age 50 years or in older women.

As La Vecchia noted, the 1974 study by Joly³ showed an effect of age at first birth and a stronger effect of parity, while the studies of Cramer,⁴ Casagrande,⁵ Newhouse,⁶ and Wynder⁷ did not show an effect of age at first birth. There is no obvious distinction between the former and latter studies in methods or populations. If age at first birth affects ovarian cancer risk, the mechanism remains to be described. However, several plausible mechanisms have been suggested to explain the widely observed relation between parity and risk, for example, through the suppression of ovulation during pregnancy and breast feeding. Further study is needed to clarify this issue.

¹LA VECCHIA C, DECARLI A, FRANCESCHI S, REGALLO M, TOGNONI G. Age at first birth and the risk of ovarian cancer. *JNCI* 1984; 73:663-666.

²MCGOWAN L, PARENT L, LEDNAR W, NORRIS HJ. The woman at risk for developing ovarian cancer. *Gynecol Oncol* 1979; 7:325-344.

³JOLY DJ, LILIENFELD AM, DIAMOND EL, BROSS ID. An epidemiologic study of the relationship of reproductive experience to cancer of the ovary. *Am J Epidemiol* 1974; 99:190-209.

⁴CRAMER DW, HUTCHISON GB, WELCH WR, SCULLY RE, RYAN KJ. Determinants of ovarian cancer risk. I. Reproductive experiences and family history. *JNCI* 1983; 71:711-716.

⁵CASAGRANDE JT, LOUISE EW, PIKE CM, ROY S, ROSS RK, HENDERSON BE. "Incessant ovulation" and ovarian cancer. *Lancet* 1979; 2:170-172.

⁶NEWHOUSE ML, PEARSON RM, FULLERTON JM, BOESEN EA, SHANNON HS. A case control study of carcinoma of the ovary. *Br J Prev Soc Med* 1977; 31:148-153.

⁷WYNDER EL, DODO H, BARBER HR. Epidemiology of cancer of the ovary. *Cancer* 1969; 23:352-370.

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TABLE 1.—RR estimates from Greater Washington, DC, 1978-81^a

Parity	No. of cases: No. of controls, by age at first birth, yr				Estimated RR	
	<20	20-24	25-29	≥30	Unadjusted	Adjusted
1	13:3	11:18	13:17	16:15	1.00	1.00
2	9:20	25:33	24:21	11:11	0.85	0.89
3-4	13:16	31:46	18:22	4:7	0.73	0.74
5+	7:14	5:11	4:2	0:0	0.59	0.51
Unadjusted RR	1.00	0.84	1.17	1.20		
Adjusted RR	1.00	0.80	1.14	0.94		(P=.10)

^aRR=relative risk.

TABLE 2.—RR estimates from Greater Washington, DC, 1974-77^a

Parity	No. of cases: No. of controls, by age at first birth, yr				Estimated RR	
	<20	20-24	25-29	≥30	Unadjusted	Adjusted
1	16:9	27:32	30:26	12:15	1.00	1.00
2	1:7	7:10	8:2	1:1	0.78	0.83
3-4	2:4	4:11	2:6	1:5	0.32	0.33
5+	0:0	0:3	1:0	0:1	0.23	0.28
Unadjusted RR	1.00	0.71	1.27	0.67		(P=.004)
Adjusted RR	1.00	0.74	1.16	0.54		

^a RR=relative risk.TABLE 3.—RR estimates from Milan, Italy, 1979-83^a

Parity	No. of cases: No. of controls, by age at first birth, yr				Estimated RR	
	<21	22-24	25-27	≥28	All	Adjusted
1-2	11:47	27:63	45:89	60:90	1.0	1.0
3-4	7:38	16:27	12:21	6:10	0.6	0.8
5+	1:28	3:10	4:3	3:2	0.5	0.8
Unadjusted RR	1.0	2.7	3.2	4.0		(P=.01)
Adjusted RR	1.0	2.5	2.8	3.3 (P<.001)		

^a RR=relative risk.

SIR: In our opinion, a reasonably reliable estimate of the effects of parity and age at first birth on the risk of epithelial ovarian cancer might be obtained by pooling the results of various published case-control studies. This could be easily done using standard methods for the combination of information from "2×2" tables¹ and hence without implicitly assuming that subjects in one study can be compared directly with subjects in another;

indeed these statistics are based entirely on comparison of cases in particular studies with controls in some of those studies. "Pooled" estimates may not be as precise and convincing as the results of a single, large study, where information can be collected in a uniform and standardized way. Nonetheless, in the presence of controversial findings, they do help giving the most reliable estimate, by minimizing random variation.

We have computed, as an exercise, pooled risk estimates for parity (1-2 vs. ≥3 births) and age at first birth (≥25 vs. <25 yr) from the four studies that, to our knowledge, gave actual numbers of cases and controls in various strata of parity and age at first birth [Cramer et al.,² our own study,³ and two reported in the above letter]. The overall risk estimates from those data (table 1) show significant independent effects both of late age at first birth [relative risk (RR)=1.40, 95% confidence interval (CI)=1.14-1.73] and of low parity (RR=1.41, 95% CI=1.06-1.67). Although the point estimates of various

¹ MANTEL N, HAENSZEL W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22: 719-748.

² CRAMER DW, HUTCHISON GB, WELCH WR, SCULLY RE, RYAN KJ. Determinants of ovarian cancer risk. I. Reproductive experiences and family history. *JNCI* 1983; 71:711-716.

³ LA VECCHIA C, DECARLI A, FRANCESCHI S, REGALLO M, TOGNONI G. Age at first birth and the risk of epithelial ovarian cancer. *JNCI* 1984; 73:663-666.

TABLE 1.—Pooled risk estimates for age at first birth and parity from four case-control studies of epithelial ovarian cancer

Study (reference No.)	No. of cases: No. of controls				Relative-risk estimates	
	Age at first birth, <25 yr		Age at first birth, ≥25 yr		Age at first birth, ^a ≥25 vs. <25, yr	Parity, ^b 1-2 vs. ≥3
	Parity, 1-2	Parity, ≥3	Parity, 1-2	Parity, ≥3		
Cramer et al. (2)	31:28	33:67	40:41	23:40	1.02	1.96
La Vecchia et al. (3)	38:110	27:103	105:179	25:36	1.93	1.06
Leshner et al., previous table 1	58:74	56:87	64:64	26:31	1.29	1.21
Leshner et al., previous table 2	51:58	6:18	51:44	4:12	1.27	2.95
Total [95% CI]	178:270	122:275	260:328	78:119	1.40 [1.14-1.73]	1.41 [1.13-1.77]

^a Adjusted for parity.^b Adjusted for age at first birth.

studies may at first sight appear different, there is no significant heterogeneity about the pooled values.

These estimates, however, are certainly unprecise, since only two levels for each factor were considered, and almost certainly biased, since they do not include all case-control studies, without material bias due to non-availability of negative results. To our knowledge, about a dozen case-control studies of ovarian cancer containing information on parity and at first birth have been conducted and published. Should the raw data on these variables from various studies be available, the interrelationships between parity and age at first birth in the etiology of epithelial ovarian cancer could probably be better understood.

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